REMARKS

Claims 1-148 and 207-236 of the present application were pending prior to entry of the Amendment above. Claims 1-5, 12-16, 25-43, 59, 67-71, 75-86, 93-98, 105-108, 110-116, 132-133, 146-148, 207-209 and 213-222 were subject to examination. Claims 6-12, 14, 17-24, 42-43, 45-49, 51, 53, 56-58, 71-74, 76-79, 87-93, 99-104, 110, 117-131, 134-145 and 223-236 were cancelled. Of the claims under examination, Claims 1-2, 4-5, 13, 15, 30, 35, 59, 66-69, 75, 80-81, 83, 85-86, 94-95, 105, 107-108, 111-113, 115, 133, 146, 207-209 and 219 were amended. Of the withdrawn claims, Claims 44, 50, 52, 54, 55, 60-62, 109 and 210-212 were amended.

The specification was amended to correct a typographical error.

Most of the amendments to the claims were made to clarify the claimed subject matter and to provide greater consistency in the claim language.

Claim 35 has been amended to recite that the heterologous nucleotide sequence(s) encodes "an antisense nucleotide sequence or non-translated RNA." This amendment is supported by the specification at page 29, lines 12-14, which recites "in particular embodiments of the invention, the nucleic acid of interest may encode an antisense nucleic acid, a ribozyme, or other non-translated RNAs, such as 'guide' RNAs" (citations omitted).

Claim 43 has been canceled and rewritten as Claim 66, which depends from Claim 59.

Claim 75 has been amended to incorporate the recitation of "mammalian" from Claim 77 (now cancelled).

Claim 80 has been amended to incorporate the recitations of cancelled Claims 78 and 79.

Applicants submit that the amendments to the specification and claims present no new matter and respectfully request entry thereof.

Although a clean copy of the amended claim set is not included in Amendments prepared under the revised amendment format, a clean copy of the

claims under examination (with the addition of withdrawn Claims 63-65) is enclosed as a separate document for the Examiner's convenience.

I. Restriction.

Applicants believe that Claims 63-65 should have been grouped with the claims of Group II and respectfully request that the Examiner substantively examine these claims as well. These claims are similar to already-examined Claims 27, 28 and 29 except that Claims 63-65 ultimately depend from Claim 59 rather than Claim 1. In addition, it appears that Claim 68 should not be grouped with the claims of Group II, and that the Examiner intended to withdraw this claim from consideration. Applicants apologize that they have not brought these issues to the Examiner's attention sooner.

II. Objections under 37 CFR § 1.75(c).

Several objections under 37 CFR §1.75(c) have been raised against the claims. The objections are addressed individually below.

Claims 4, 5, 14, 15, 30, 68, 86, 107, 108, 110, 112 and 209 stand objected to for being in improper dependent format. The Office Action states "the claims are attempted to be written so as to lack adenoviral regions such as E1, E3, or IVa2, wherein the regions were clearly embraced by the recited genome of the base claim" (Office Action, page 3, lines 3-5). The Applicants are somewhat unclear about the basis of this objection, but believe that the objection is that the recited "genome" in the independent claims requires the inclusion of the E1, E3 and IVa2 regions and the like, *i.e.*, these regions cannot be deleted from a "genome." Applicants have amended the independent claims to recite an "adenovirus vector" and a "recombinant adenovirus genome" to clarify that the invention is directed to adenovirus vectors comprising recombinant (*i.e.*, genetically modified) genomes and not a wild-type genome. Thus, one skilled in the art would readily understand that the claimed adenovirus vectors comprise recombinant genomes that may not include

all of the regions of the wild-type adenovirus genome. Indeed, E1-deleted and E3-deleted adenovirus vectors are standard in the art.

A similar objection appears to apply to Claim 30, which recites a recombinant adenovirus vector comprising "5' and 3' adenovirus inverted terminal repeat sequences, an adenovirus packaging sequence, and an adenovirus E1A enhancer sequence." Applicants note that a recombinant adenovirus vector can contain the native adenovirus terminal repeats and packaging sequence or synthetic versions of these sequences. Nonetheless, to reduce the issues and to expedite the prosecution of this application, Applicants have omitted these recitations from Claim 30, and note that Claim 1 encompasses both synthetic and native sequences. With respect to the E1A enhancer, this sequence is found in the same region as the packaging sequence and is therefore generally included in current adenovirus vectors, but it is not necessary to do so. Accordingly, Claim 30 retains the recitation of the E1A enhancer.

Claim 133 stands objected to on the basis that it is a substantial duplicate of Claim 1. Claim 133 has been amended to recite a composition comprising a plurality of adenovirus vectors produced according to the method of Claim 105, thereby better distinguishing the subject matter of Claim 133 from the subject matter of Claim 1.

Claims 1, 59, 75-77, 105 and 146 stand objected to for reciting non-elected subject matter. Claims 76 and 77 have been cancelled. The other claims have been amended to omit the non-elected subject matter, thereby addressing this objection.

Claims 1-5, 12-16, 25-43, 59, 67-71, 75-77, 86, 93-98, 105-108, 110-116, 132-133, 146-148, 207-209 and 213-222 stand objected to for reciting "comprising one or more deletion(s)." This objection appears to be on the basis that the claims include a negative recitation, *i.e.*, the claimed genome cannot comprise something that is absent or deleted.

Applicants respectfully note that the Court of Appeals for the Federal Circuit has stated that "[t]he use of a negative limitation to define the metes and bounds of the claimed subject matter is a permissible form of expression." *Animal Legal*

Defense Fund v. Quigg, 932 F.2d 920, 923 (Fed. Cir. 1991). Moreover, the use of the term "deleted" adenovirus (or equivalent language) is standard in the art and in issued U.S. patents (*see* as a few examples, U.S. 6,063,622; US 6,287,571 and U.S. 6,426,216).

The Applicants appreciate the Examiner's efforts with respect to this application and the suggestion of a more condensed claim language. The Applicants have adopted the Examiner's suggestion and have amended the independent claims to recite "lacks a coding sequence for a functional 100K protein." Applicants note for the record that this claim language does not require that the virus lack the entire 100K coding region, but only that the recombinant viral genome does not express a functional 100K protein. Applicants further note for the record that these amendments are not narrowing.

Several of the dependent claims still recite "deletions." However, Applicants have amended the claim language to address the Examiner's concerns regarding negative recitations.

In view of the foregoing, Applicants submit that the objections to the claims under 37 CFR 1.75(c) have been addressed and respectfully request withdrawal of the objections on this basis.

III. Enablement.

Claims 69-71, 78-86 and 93-95 stand rejected under 35 U.S.C. §112, first paragraph for lack of enablement. This rejection is respectfully traversed below.

With respect to Claims 69-71 and 78-86, the Office Action contends that the specification is only enabling for "mammalian" producer cells and "isolated" cells. Claim 69 has been amended to incorporate the recitation of a "mammalian" cell from Claim 71. Accordingly, Claim 71 has been cancelled. With respect to Claim 78, Applicants note that the specification clearly enables a cell other than a mammalian cell that comprises an isolated DNA encoding an adenovirus 100K protein (*e.g.*, the working examples demonstrate a bacterial cell containing such a DNA).

Nonetheless, to expedite the prosecution of this application to allowance and to reduce the outstanding issues, Claims 78-79 have been cancelled, and the recitations of these claims have been incorporated into Claim 80.

Further, Claim 80 (from which Claim 81 depends), which is intended to encompass a cell for producing 100K- adenovirus vectors, has been amended to recite an "isolated" cell.

With respect to Claims 69-71, Applicants submit herewith a copy of Hodges et al., "Adenovirus vectors with the 100K gene deleted and their potential for multiple gene therapy applications," *J Virol.* **75**:5913-20 (2001). This publication demonstrates administration and expression of a 100K- adenovirus vector *in vivo*, thereby supporting the enablement of both cultured cells and cells *in vivo*.

Claims 93-95 further stand rejected on the basis that "the as-filed specification only teaches an adenovirus genome that lacks the nucleotide sequence coding for a functional adenovirus 100K protein, when used in the context of an adenovirus helper virus or a propagation-defective adenovirus genome" (Office Action, page 5, last paragraph). While Applicants do not agree with this rejection, in order to expedite the prosecution of this application to allowance, Claim 93 has been cancelled and Claims 94-95 have been amended to recite an isolated DNA comprising a "recombinant adenovirus genome" that lacks a coding sequence for a functional 100K protein.

In view of the foregoing amendments and remarks, Applicants submit that the claims satisfy the enablement requirement of §112, first paragraph and respectfully request withdrawal of the rejections on this basis.

IV. Indefiniteness.

Claims 81, 82 and 93 stand rejected under 35 U.S.C. §112, second paragraph as indefinite. The Office Action states that the recitation of "packaging" cell in Claim 81 does not have proper antecedent basis in Claim 78. This rejection also applies to

Claim 82, which depends from Claim 81. The term "packaging" has been deleted from Claim 81. Further, Claim 93 has been cancelled.

Accordingly, Applicants submit that the claims satisfy the requirements of §112, second paragraph and request withdrawal of the outstanding indefiniteness rejections.

V. Art Rejections.

Claims 78-82 stand rejected under 35 U.S.C. §102(e) for anticipation and/or under 35 U.S.C. §103(a) for obviousness over Reddy et al. (US 6,492,343), Slemenda et al. (*Nucleic Acids Res.* **18**:3069 (1990)), and/or Oosterom-Dragon et al. (*J. Viol.* **33**:1203-1207 (1980)). The individual rejections are addressed below.

A. Reddy et al.

Claims 78-80 stand rejected under 35 U.S.C. §102(e) as anticipated by Reddy et al. Claims 78-79 have been cancelled. Claim 80 recites an isolated mammalian cell that "can propagate an adenovirus genome that essentially lacks expression of a functional 100K protein." Reddy et al. does not disclose an isolated mammalian cell that can propagate (*i.e.*, transcomplements) an adenovirus genome that does not express a functional 100K protein. Moreover, the claimed subject matter is not suggested by the cited Reddy et al. patent. Accordingly, Applicants submit that the subject matter of Claim 80 is both novel and nonobvious over the cited reference, and respectfully request withdrawal of the rejection under §102(e).

B. Slemenda et al.

Claim 78 stands rejected as anticipated by Slemenda et al. "as evidenced by Reddy et al.," although the rejection cites §103(a). This rejection is moot as Claim 78 has been cancelled, and it is requested that the rejection be withdrawn. Applicants are enclosing a complete copy of the Slemenda et al. reference for the Examiner's convenience.

C. **Slemenda et al. in view of Oosterom-Dragon et al. and Reddy.**

Claims 78-82 stand rejected under 35 U.S.C. §103(a) for obviousness over Slemenda et al. in view of Oosterom-Dragon et al. and Reddy. Claims 78-79 have been cancelled. As discussed above, Claim 80 is directed to a mammalian cell comprising a nucleotide sequence encoding an adenovirus 100K protein, wherein the cell "can propagate an adenovirus genome that essentially lacks expression of a functional 100K protein." Claim 81 is drawn to stably transformed mammalian cell, and Claim 82 specifically recites a K-16 cell. None of the cited references taken alone, or in any combination, disclose or suggest a packaging cell for producing 100K- adenovirus vectors. Accordingly, Applicants submit that the subject matter of Claims 80-82 is novel and nonobvious over the cited references, and respectfully request withdrawal of the outstanding rejection.

VI. Double-Patenting.

The claims stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 8-14 of US 6,328,958. In response, Applicants submit herewith a terminal disclaimer in compliance with 37 CFR § 1.321 with respect to U.S. 6,328,958. Applicants note that the submission of this terminal disclaimer in no way represents an acquiescence to the outstanding rejection or an acknowledgement that the subject matter of the pending claims is obvious over the cited claims of U.S. Patent No. 6,328,958.

Accordingly, Applicants respectfully submit that the filing of a terminal disclaimer has obviated the outstanding double-patenting rejection, and respectfully request withdrawal of the rejection on this basis.

VII. Conclusion.

The concerns of the Examiner having been addressed in full, Applicants respectfully request withdrawal of all outstanding rejections and the issuance of a

Notice of Allowance forthwith. The Examiner is encouraged to address any questions regarding the foregoing to the undersigned attorney, who may be reached at (919) 854-1400.

Respectfully submitted,

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Attachments:

Hodges et al.
Slemenda et al. (w/IDS)
Terminal Disclaimer
Clean copy of claims under examination

CERTIFICATE OF EXPRESS MAILING

"Express Mail" mailing label number: EV318418285US Date of Deposit: October 14, 2003
I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Sloan Smith